DRUG INFORMATION ASSOCIATION

FDA/DIA SCIENTIFIC WORKSHOP ON FOLLOW-ON PROTEIN PHARMACEUTICALS

BREAKOUT SESSION D

CLINICAL PHARMACOLOGY STUDIES

Monday, February 14, 2005

1:30 p.m.

Marriott Crystal Gateway
1700 Jefferson Davis Highway
Arlington, Virginia

PARTICIPANTS

MODERATORS:

DENA HIXON, M.D.

HAE-YOUNG AHN, PH.D.

HONG ZHAO, PH.D.

DAVID PARKINSON, M.D.

WILLIAM SCHWIETERMAN, M.D.

P R O C E E D I N G S

DR. HIXON: We're a little after our starting time, so we need to get things underway here.

I'm Dena Hixon. I'm the Associate Director for Medical Affairs in the Office of Generic Drugs. And I'm Acting as the lead FDA moderator of these sessions this afternoon.

I want to start out with just some basic ground rules and background information here.

In contrast to the open public hearing that was held in September, this meeting is intended to solicit open scientific discussion from the audience. We have an official transcriptionist present to accurately record the proceedings of the meeting. Any person wishing to provide comment at this meeting is asked to use the microphone in the aisle, and to clearly state your name and your affiliation.

We would like you to also, if you have a business card, as soon as you're finished talking, provide your business card to the transcriptionist.

If you do not have a business card, please print your name and affiliation on one of the note pads on the table so that you can provide it to her as soon as you're finished talking.

We want to remind you that this is intended to be an exchange of scientific information and ideas regarding the information needed to evaluate a protein product that purports to be the same as a product already on the market, and no longer protected from competition by a valid patent or exclusivity. This is not intended to be a debate about whether there can be or should be an abbreviated mechanism for bringing such a product to the market.

We ask each individual to keep your comments brief--to approximately two or three minutes, if possible. If you're not finished by that time--particularly if we have a whole line of additional people wanting to speak--the Chair reserves the prerogative to ask you to relinquish the microphone.

And also, if you present any--if you

discuss any scientific data that has not previously been submitted to the docket, we ask the individual discussing that data to present it to the docket. And that docket number, for those of you who may not have it, is 2004N-0355.

We also want to remind the audience that FDA has no established policy with regard to the issues at hand. No discussions by an FDA person should be represented as agency opinion or policy, but rather the observations or opinion of the individual making the statement.

For this session, and for the repeat session to follow this afternoon, we have two additional FDA moderators: Hae-Young Ahn, who was one of the speakers in the preceding plenary session. And Hae-Young is a team leader in the Office of Clinical Pharmacology and Biopharmaceutics in CDER. And she works predominantly with the Division of Metabolic and Endocrine Drug Products.

During this session Dr. Ahn will record highlights of the discussion on the laptop, and

we'll use that in place of a flip chart, because it's more visible. And she may also assist in asking for clarification from speakers as needed, to assure accuracy in the summary of the breakout session.

Dr. Hong Zhao is a senior reviewer of Clin-Pharm and Biopharmaceutics in CDER. She's reviewed numerous neuropharmacology drug products, and has received numerous awards in CDER. She has made some presentations--"Clinical Pharmacology Considerations: A Case Study"--at the FDA Workshop on Proteins and Peptides, Scientific Foundation for Review in 2004, and she also recently lectured on pharmacokinetics of large molecules and biotech-derived products for an FDA course on pharmacokinetic and toxicokinetic concepts.

During this session, Dr. Zhao will be taking comprehensive notes, asking for clarification, and posing additional questions as needed. And she will be helping with the wrap-up session this evening to provide a summary to the plenary session, which will actually take place

Wednesday morning instead of tomorrow morning.

We have Dr. David Parkinson here. Dr. Parkinson is probably well known to many of you.

[Pause.]

I'm sorry, I've lost my place here.

Dr. Parkinson is--

DR. PARKINSON: Well known for unknown reasons.

[Laughter.]

DR. HIXON: I'm sorry. [Laughs.] He is vice president of Global Development and head of the Oncology Therapeutic Area at Amgen. Dr. Parkinson is Canadian-born, and received his M.D. degree from the University of Toronto School of Medicine, and followed that with fellowship training at McGill University. And since then, his career has led him to positions of leadership at Tufts New England Medical Center and the M.D. Anderson Cancer Center and the NIH, prior to working for Novartis--right?--

DR. PARKINSON: Correct.

DR. HIXON: --and now with Amgen.

We also have Dr. Bill Schwieterman, who is

an independent consultant with a long history in PK and PD evaluation in CBER at the FDA. And he is currently working as an independent consultant in Mobile, Alabama.

What I would like to do is ask each of our industry moderators to present a brief introductory discussion, with a couple of slides, and then we'll open the floor to audience questions and discussion.

Dr. Parkinson.

DR. PARKINSON: Thank you, Dena. As you were giving my biography, I was just waiting to see how it was going to turn out.

[Laughter.]

Can you just click that for me?

That requires technical skills that--

[Slide.]

Great. Thank you.

Good afternoon. I'm David Parkinson, and what I'd like to do is really just give a very brief perspective--before giving it over to Bill--to try to put a context around the discussion

this afternoon.

This morning's talks I think were excellent in doing that. But just some thoughts from my own perspective. I'm not a card-carrying PK/PD person. I'm not a clinical pharmacologist--I want to say that right now--but I am a clinical drug developer on the innovator side, and we deal with these issues a lot, and we care about them a lot.

So, the kinds of information that I heard this morning leads me to think in the following way. And I present these not as positions but as observations, as part of the conversation we should be having this afternoon.

[Slide.]

It's pretty clear that biotechnology products--perhaps much more so than small molecules--are process-dependent products. Everything we heard this morning points in that direction. And although it was quite clear to me, listening sometimes in awe of the wonderful technology that allows us to characterize these

proteins, that although we have an approved and improved, it is somewhat limited ability to describe a biological completely through analytical and biological characterization.

[Slide.]

So recognizing those limitations of analytical specifications, and these kinds of assays as valid predictors of ultimate biological safety and potency--and that's where I think we should have a lot of discussion this afternoon--really makes me aware of the limitations of physical-chemical testing to establish sameness. And that's very important to us as clinicians.

[Slide.]

So that tells me, just from that train of thought, that PK studies, where feasible--and I think we heard from everyone that they're largely feasible--are essentially necessary in most situations as part of any process to characterize a new biologic; the need to confirm dose in order to not put patients at any great risk.

Now, I think we heard some very

interesting information this morning that, frankly, PK studies may be necessary, but they may very well not be sufficient. And I think, again, something we should get into in more discussion this afternoon.

[Slide.]

So it seems pretty clear from a lot of the work that I heard this morning about the necessity and the value of parallel PD studies, together with PK studies--certainly in settings in which validated surrogates for efficacy do exist.

The limitations of PD studies in the absence of validated surrogate--I mean, I'm not sure what you would do in that setting. I would point out to you that, frankly, how many surrogates are actually validated? Precious few.

That tells me that at least some clinical data is required. And I must say I listened this morning, and it will be a very interesting point of discussion this afternoon, to understand why doing the PK study could be unethical while release of an agent to a larger population would not be. So--I

just could not follow that logic. Just to put it on the table.

And the reality is that very limited clinical experiences have very limited value. I speak as a drug developer. I do this for a living, and I know how hard it is to sort biologicals out in the clinic, in the context of diverse patient populations, diverse diseases--and usually diverse therapeutic settings. Because these drugs are rarely used in isolation.

So I raise these kinds of thoughts as a context for further discussion this afternoon.

Thanks very much.

Bill?

DR. SCHWIETERMAN: Thank you, David. I'm going to be very brief, actually.

Dr. Hixon called me last week and said, really, the purpose here is to get the discussion going, and to be up front about what the scientific issues are. And that's what I intend to do.

I guess just a comment beforehand: I think the one thing that I would recommend during these

discussions is that--as Dr. Kozlowski, I think, wisely pointed out, that the boundaries of each person's perspective need to be specified when discussing the utility or assertions or whatever with regard to PK studies.

It seems to me that this is, a) an enormously complicated area, and therefore one where you can wind your way around without really coming up with any definitive conclusions, unless those boundaries are specified; and, b) that when discussing the PK data, it has to be done in the context of other data; and the other data that's come before it and after it. Because I'm not sure that one size fits all here. I'm not sure that any individual question can be addressed that actually addresses the whole field.

So those are just some general observations. And for that--and since I have a minute or two to talk--what I did was simply lift slides that were done from the plenary session, and see if, in fact, we could have a scientific discussion around some of the tenets brought

forward.

[Slide.]

So one of the slides that I saw was "Demonstrating Comparability Across the Spectrum of Protein Comparisons" is one that's related to complexity. And, going from low complexity to high complexity changes the utility of PK/PD studies; in fact, changes the utility of all studies that are done to characterize follow-on biologics.

So I would say that, given this as an assertion, that we discuss the meaningfulness of this and how it might be utilized in conclusions that are drawn.

So, the considerations for discussion then are as follows.

[Slide.]

"PK studies provide information about comparability in systemic exposure"--talk about the limitations and usefulness of this statement.

"PK studies are feasible for a majority of proteins."

"PK studies may not be needed for

solutions of simple protein products that are comparable analytically." What are the merits of this particular argument?

"PK studies are generally necessary if uncertainty about comparability could not be adequately minimized through characterizations of animal studies."

I think all these points have merit. I think we need to discuss how much merit, and where they fit.

[Slide.]

Last slide, then: "The standard 90 percent confidence interval for bioequivalence criteria are appropriate for most PK studies." Is this, in fact, what the group here believes?

"The usefulness of PD studies is, in part, a function of available outcome measures."

"If PD measurements are to be included, simultaneous PK/PD studies are often preferred."

And then, finally: "PK/PD studies, in conjunction with adequate characterization are usually sufficient to support approvability, and in

some cases interchangeability."

I think all of the things that were stated in the plenary session, they're very useful. And this isn't to criticize these; these are to frame these around specific instances that might be then useful for drawing conclusions, once we actually get into the details.

Thank you.

DR. HIXON: Okay, the floor is open for any comments or questions, or discussion from the audience.

Please make sure you state your name and affiliation, and provide that in writing to the transcriptionist.

DR. SANDERS: Hello. My name is Steve Sanders--I'm an independent consultant--just a couple of thoughts that I had as I listened to the presentations this morning, with regard to the clinical studies--PK/PD studies--that might be needed.

You know, segueing from the current situation with generic products to biologicals, the

underlying assumption, I think, is that you have a very good understanding of the chemical characterization and biological activity of the molecule that you're working with, and then you're going to take that, and you're going to put it in human beings. PK, in itself, is really an evaluation of the dosage form. And in many cases that's what it's been used to evaluate, in a setting where you have the assumption that if you deliver this molecule into the bloodstream, and measure the concentration, that you're going to have a myriad of effects that take place downstream from that. But your assumption is there.

And so you're looking at the dosage form. And as we heard this morning, even though there may be an argument that a simple solution wouldn't require a PK study, I think probably the consensus is that a PK study would at least be a minimum that you would certainly want to do, regardless of how the drug is administered. So, does the dosage form get that molecule into the bloodstream?

The problem that you encounter with

biologicals at times is that the way that these are measured may be inherent in the biological activity itself. You can have an assay that relies on some measure of some part of the molecule that may or may not reflect its activity. But, nevertheless, you get some PK. That problem should be covered by biological characterization of the molecule, hopefully in some in vitro or in vivo or pre-clinical type of analysis.

So that's dosage form for PK, as oppose to a real biological effect, because there are so many assumptions.

For PD, I was glad to hear Dr. Parkinson mention the issue about surrogate markers versus endpoints. I mean, in my mind, pharmacokinetics is creating a relationship between the drug being in the body in some way, and the clinical outcome that you want. And the best PD marker is your clinical outcome. You know, the example was given of insulin and blood glucose. Well, you measure blood glucose, that's what you want to happen when you administer insulin.

In many cases now we have surrogate markers, and certainly the comment that Dr. Parkinson made is valid, where, you know, the

relationship between how valid that surrogate marker is, and the clinical endpoint that's important for the patient, that's going to be dependent on the individual molecule that you're working with.

So those were just a couple of comments that I wanted to make.

DR. PARKINSON: Any feedback, with respect to those comments, from anybody else in the audience before we go on to another thing? Thank you very much.

Mark?

DR. ROGGE: Mark Rogge, ZymoGenetics. And I guess I would want to be clear: you're saying the PK is only a measure of the dosage form? Or is it also a measure of the components of what's in the product, as well?

VOICE: [Off mike.] [Inaudible.]

DR. PARKINSON: I think you may need to use

the microphone--or somebody will probably call the police.

DR. SANDERS: That's going to depend a lot on the assay, I think, that you have developed, as to what you're measuring. The assay will tell you what you're measuring. But as far as, you know, once you establish what you're measuring, then you can determine what it is that's actually floating around in whatever bodily fluid you happen to be doing your PK on.

So, I don't know if that really answers your question.

DR. ROGGE: Yes, I'd just like to see that first point expanded; that it's not only a measure of the performance and the dosage form, but it's a measure of the characteristic of the product, as well. Because there may be some changes. You may see some change, potentially, in a clearance or some other measure that may not have anything to do, per se, with the dosage form itself. It's simply a component of the product that's now shown up, or maybe was there to begin with, but it's now

in a higher concentration, or higher percentage.

DR. SANDERS: You know, I think if that were the case--if you saw some differential in clearance or the way the physiology is with the molecule--then you would try to relate that to some physical-chemical characteristic, and go back, really, to the pre-clinical setting, or the chemical setting to really understand why that's happening. And you may not have an identical molecule.

DR. PARKINSON: Next question.

DR. FIELDER: Is it okay to use your overhead?

DR. PARKINSON: Sure.

DR. FIELDER: Paul Fielder--I'm Director of Pharmacokinetics and Pharmodynamic Sciences at Genentech.

I sort of had the--I guess--the benefit of coming at this from a very biological point of view--I was pretty much a Ph.D. biologist who came into a PK/PD group, so I came much more from the PD side, and then learned PK.

And I think one of the basic premises we've heard today from people saying with the biogenerics, "If we understand the mechanism of

action, then we should be able to use PK/PD to test to see whether a drug's going to be safe and efficacious." And I've probably studied growth hormone for 20 years, and that's probably the most studied molecule there is, and I don't think anyone knows the true mechanism of action--or all the actions--of something as simple as growth hormone.

So I think from our experience, especially of more complex biologics, bioequivalence is really inadequate. And pharmacokinetics are not a valid surrogate for clinical effect in most biologics. I think we're measuring what we can see. We're not measuring the concentration of a drug at the target tissue, or its effect at that tissue. So it's really, we're looking where the light is. So it doesn't really have a true bearing on the pharmacological target.

I personally think pharmodynamics are great. They're wonderful for making decisions

whether to move a drug forward, and to establishing safe and efficacious doses. But, again, they're unreliable surrogates for clinical efficacy and safety.

We've had many instances where we have some rare side effects, or safety occurrences, with some of our antibodies. There's no PK or pharmodynamic measure that tells us that. We can also hit our PD endpoints with, say, Rapteva, where 100 percent of the patients we achieve adequate PK and PD response, and have, you know, a Patsy 75 in about 40 percent of the patients.

So, even achieving the same PK/PD is not enough, because it's really not reflective of the true mechanism of efficacy. Some are better than others. I think we'd all agree: hemoglobin A1C, which is really a surrogate endpoint--and one of the few ones--is good for an insulin. So if you did a one-year study and measured hemoglobin A1C, I think we'd accept that.

And I think, so, really, if the key point is safety, and not short-cutting safety, then this

is a good way to help people get to pivotal trials. But in no way should it really replace a pivotal trial.

DR. SCHWIETERMAN: Let me ask this in the spirit of making this an open discussion--because I don't have a position either way--but if you're going to view these problems of interpreting PK/PD studies, it's important that you actually understand the question being asked. And if the question is actually predicting clinical outcomes--you, of course, are absolutely right. But if the issue actually is showing comparability to the product, based upon an overall data set, then the PK/PD data may actually play a different role and, in fact, be more relevant in certain settings.

So I guess my question to you is: do you see utility for PK/PD studies in other veins, irrespective of their predictability alone, for clinical outcome measures?

DR. FIELDER: Well, I put this the same way I put animal studies. And there is--the generics

want to say, "Well, let's do PK/PD in animals." And I don't think any PK/PD scientist would say PK/PD in animals is anywhere near reflective of humans.

I think it's a very good tool. And, yes, you could use it. And if someone came and showed they were different, I'd clearly say, "You have a problem." If they came and said they were the same, I'd say, "Well, you can move to the next step of testing." That's how we use it.

You know, if we see something different, we know we have a problem. If we see something that looks the same, we know we can go to the next step.

DR. SIEGEL: Jay Siegel, Centacor.

I'd like to explore in a little more depth that issue of surrogates, and validated surrogates, because while it's true that few surrogates are validated for efficacy, I think--as your question presupposes, Bill--we may be talking, in this setting, about asking something a little bit different from a surrogate, and validating it for

efficacy.

First of all, validation of a surrogate is not a black-and-white thing. A surrogate usually will work for a drug or a class of drugs. And the broader you get away from that class--the further you get away--the less you know. So if someone talks about glucose and insulin, I would say--for example, if somebody came forward with an enzyme that broke down glucose, or an antibody to glucose, and showed that it had the same effect on postprandial glucose as does insulin, one would hardly think that meant it was effective for the treatment of diabetes. If one came up with an insulin variant, and it had the same glucose effect, one might think, "Well, that's interesting." That's more interesting. It tells you more. It doesn't answer a lot of questions about clinical cohorts, about chronicity, about immunogenicity, about side effects perhaps. If one came out with a very similar insulin, one that by all testing is indistinguishable from another insulin, and it has the same glucose parameters,

one might say that one could draw further conclusions from that. In a sense, the innovator product data helps validate the validity of a surrogate for that particular product if that data is, in fact--and I won't go into whether it's legally available--but if that data is available to use, some of the risks of using surrogate are smaller by knowing that you're dealing with a molecule that is very much like another molecule.

That said, I think there's a huge number of things you don't know. Because even at best, once you're there you can say, for a particular desirable effect, such as lowering circulating glucose, you know that you have an effect similar to an innovator. But there are many other effects that a biological has. I won't go into great detail, because I will have the opportunity to speak tomorrow on these issues.

But there are going to be a bunch of other issues around safety, around immunogenicity, around other effects of a drug.

So I think we need to look carefully at

these markers. It's not just: if it's validated you can use it, and if it's not, you can't. I think they have a use, but I don't think they get us there, in terms of providing the clinical data we need.

DR. PARKINSON: Good. Other comments?

Yes, sir. You're on.

VOICE: [Off mike.] [Inaudible.]

DR. PARKINSON: You're allowed to have another issue.

[Laughter.]

DR. CHATTERJEE: My name is D.J. Chatterjee. I'm a reviewer with the FDA.

Well, it's on the general theme on the validation of the markers. In my line of work I work with two common indications; one for which the endpoints are--I mean the surrogate endpoints can be evaluated, are very straightforward. But in the other one, it's more difficult. The clinical trials are very long, very complicated, and it's very difficult, in terms of recruitment purposes. And the surrogate endpoints I don't think are even

close to being validated.

So, we almost always see, even for a minor change in formulation, we have to ask for a Phase III--a full safety and efficacy trial--which, the trial itself might take two years, and recruitment is an additional burden.

So I wold like to hear some discussion on any other thoughts that could be--

DR. PARKINSON: Okay--so that's a very interesting issue for discussion: the issue relates to same molecule, or same potential comparator molecule, but different biological/clinical settings, and could you translate information from the one setting, which is easy to study, to the other setting which is less easy to study?

Do I summarize that?

Well, it was a first pass.

[Laughter.]

DR. CHATTERJEE: The first one, in which the indication--the endpoints are very well correlated, I think we can--even the endpoints, where the endpoints generally are always clinical

pharmacology. We have a handle on that.

There's another indication I'm talking about, in which the endpoints are not--the surrogate endpoints are not validated. And the clinical trials are extremely complicated, and recruitment is a big issue--

DR. PARKINSON: Yes.

DR. CHATTERJEE: --so in that indication, can we have some discussion on what else can be done to simplify the registration process?

DR. PARKINSON: Well, that's what I just indicated. So, as a drug developer who's trying to get over the hurdle in a responsible manner, I would try to go for the easier one and get over it. The issue is whether it's relevant or not.

It's certainly not relevant in registration. And it's increasingly not relevant in reimbursement. But the issue is: is it relevant in determining comparability, and then extending the potential applications?

So that's a really interesting topic for discussion. What do people think?

[No response.]

DR. PARKINSON: In the absence of a rapid response, my first thoughts--

[Laughter.]

--are that it relates to how complex the biology is, and how similar the purported mechanisms of action might be from that simple clinical setting with an easy read-out, versus the more complicated clinical setting to study, with its read-out.

And I think that that's where judgment might come in, with respect to--what you're talking about is extrapolation from an easily studied situation to a more difficult situation for study.

What do people think about that? Somebody's thinking.

DR. BEN-MAIMON: Hi. I'm Carole Ben-Maimon from Duramed Research.

My question is really: what is the relevance of that discussion to what we're talking about right now?--with all due respect. We're not talking about new products or new indications.

We're talking about the comparability of products from different manufacturers.

And so I think it would behoove us to sort of focus, really, on the issue of comparability here, and the fact that what we're looking for are identification of differences between two products, starting with analytical methodology; looking at differences. And we've all agreed, I think, we heard very clearly this morning, that the differences can be identified through analytical methods. Analytical methods are actually more sensitive than PK/PD or clinical trials.

And so what we're really looking for is to ask the question: whether, when we see differences in analytical methodology, and we see differences between two products that we think should be comparable, can we answer the question of whether or not there's clinical relevance, and can we then move on to PK, ultimately PD? And if we're still seeing differences, then I would venture to say that ultimately we may conclude that the products are different, which is an okay conclusion.

The other thing I would ask the gentleman from Genentech if he could clarify, is whether or not every company who's doing comparability

protocols ultimately does a Phase III trial? Because it's our understanding that manufacturing changes are made. And when you go through a certain process and you don't identify differences, you see that there are similarities, at some point you do stop, and you say, "Okay. We've done due diligence. These products look to be comparable. They look to be essentially the same. And the significance of whatever limited difference we're seeing, we do not believe are clinically relevant."

And so I would like--I would hope that we as a group could focus the conversation on--

DR. PARKINSON: Okay. We certainly--that is the topic for the afternoon, but I won't let you avoid that last one, because the issue is: is an agent which is quite comparable, even with a clinical read-out in one clinical setting, necessarily extrapolatable to another clinical setting where the biology--the underlying

biology--may be actually different?

And I actually think that's quite a relevant clinical situation, because we see this all the time. The complexity of clinical medicine is not that simple. So I actually think it is a relevant topic for discussion--notwithstanding your other comments, which I appreciate.

Okay?

DR. BEN-MAIMON: Yes, I'm also a drug developer, and also familiar--

DR. PARKINSON: Right. So you know.

DR. BEN-MAIMON: So we have similar interests. Clearly. And clearly none of us have any intention of trying to put drugs on the market that either aren't comparable and haven't met the standards that all of our products meet today.

But I would venture to say that that kind of situation is a decision that needs to be made on a product-by-product basis.

DR. PARKINSON: Fair enough.

DR. BEN-MAIMON: And if there really are significant differences in the biology, then maybe

there's a different PD parameter, or a different technology that needs to be applied through the analytical methodology. Or maybe it's in PK you're looking for something different.

But those types of issues don't preclude the fact that you--or require you ultimately to do a clinical trial. You can use the science that's developed over time, through the experience that's developed as products are out on the market for long periods of time.

And we also shouldn't forget that it is a benefit-risk assessment. If we require--the agency, in all its hard work and, quite honestly, in the really important work they do for us as citizens of this country--to have no choice, no even sense that there could possibility be any untoward outcome from approving a product, we'd have no drugs on the market. Because we all know that drugs and biologics have issues with them, and it's a benefit risk--

DR. PARKINSON: Yes, I doubt if anybody in the room would disagree with you. There clearly

needs to be a path for approval of follow-on biologics. The issue is: what should that path look like, and what should the standards be for the various pieces?

Did that answer help you a little bit with the extrapolation to the second indication? I'm just trying to be a responsible moderator here.

DR. CHATTERJEE: I'll simplify the question.

DR. PARKINSON: Okay. [Laughs.]

DR. CHATTERJEE: We heard a lot of PK/PD modes of not doing a clinical trial. Can that be extrapolated to a complicated situation like that? That's the question.

DR. PARKINSON: Okay--what do people think?

DR. SANDERS: Maybe I'll save everybody a lot of time. I'll just say: "No."

[Laughter.]

DR. PARKINSON: Okay.

DR. FIELDS: Can I please answer the question?

DR. PARKINSON: Sure.

That was the first speaker. So the very first business card you have.

DR. FIELDS: All right. I'm going to

answer the lady from Duramed, plus add one to the last discussion.

We do not do formal bioequivalence every time we make a minor process change. Sometimes we have to. It really depends on negotiation with the FDA.

Again, where we use PK/PD a lot is a tool to see, within our manufacturing process, are we making a consistent process? We don't use it to go outside major changes, or other drugs. It's clearly another measure we use to make sure we're keeping our process in line.

We do not, you know, know exactly what we see, how relevant that is to safety or efficacy anyway. But it's relevant to how consistent we make the drugs, and that's why we use it.

And we've many occasions--and I've spent years doing this--where a very minor process change, the FDA's required us to repeat Phase III

trials and do formal bioequivalence trials. So, I would hope they hold the same rigor to the follow-on biologics that they's done with us innovators.

The second question--whether you can take data from one indication to another--I'll give a few examples.

Probably the most--the one that will soon be published--we've published some of this--is using growth hormone replacement therapy in adult men or women. It turns out that you need twice the dose in women, because they take oral estrogens a lot, and that inhibits the action of growth hormone. So if you naively went dosing--which they've been doing for years--women get undertreated. So you do need to study the drug in any new indication, especially similar.

I think the biggest one, where we got a big wake-up call, was when Pharmacy at Upjohn started taking growth hormone and trying to expand its indication into ICU patients, and ended up killing quite a few patients unnecessarily when

they unblinded the trials and found out that growth hormone, in a certain clinical situation, actually increases mortality.

So, again, I don't think anyone can say they know how even a simply protein like growth hormone works, or where it will be safe and where it will be unsafe.

DR. SCHWIETERMAN: Yes, those are very useful comments. I want to make one follow-up statement just for the group, because I think this might be informative.

The question here isn't really one of establishing identity since, in Western science, you don't ever show something absolutely. It's rejecting the alternative hypothesis that the two are different. And I'm just talking, you know, big, broad picture about a possible path.

So the issue on the table isn't really the positive predictive value of any one particular measure for showing clinical identity, it's the positive predictive value of that particular measure for ruling out any significant differences.

And so when we discuss PK/PD studies--I mean, this is the way non-inferiority studies are done--we need to keep that notion in mind that,

really, we're operating under a certain level of priors, or certainty about the existence of differences, and then going on to the next study to actually address that.

And so it seems to me that if we frame it in that kind of a light we can get at some of these difference. Anyway, I just want to throw that out for discussion.

DR. ROGGE: Mark Rogge. I was here earlier, and I just had one comment and it goes back to what Carole had mentioned before. And I want to make sure I was correct on what you said.

This morning we saw data that showed that, you know, the manufacturing--CM and C technologies are more sensitive than clinical trials.

You didn't say that?

DR. BEN-MAIMON: [Off mike.] [Inaudible.]

DR. PARKINSON: Would you mind coming up and use the microphone, please?

DR. BEN-MAIMON: What I said was that when taken together, the analytical methodologies and chemical characterization methods that we have today can actually detect, in a much more sensitive way, specific changes between two--when comparing two different molecules; and that those differences

may or may not translate into clinically relevant outcomes. And the clinical trials are much less sensitive in detecting what may be insignificant differences between two particular compounds, or two particular molecular structures; and that the analytical methods actually--the question, I think, that's really going to need to be answered as we move forward with this process is: when you see differences, are they clinically relevant?

DR. PARKINSON: Right.

DR. SIEGEL: I want to return to the question: if you have two products that might have some differences, and they're comparable in one clinical setting can you assume that they're comparable in all clinical settings?

There's actually many examples--many

counter-examples to the assertion that they would be. There are many differences amongst products in the same class that are undetectable that do not show up in one clinical setting and do in another setting.

You know, when you talk about larger differences, you can talk about products in a class such as the anti-TNFs, in which there are three major products on the market that in some indications look identical, but in some aspects of their safety and efficacy profile are quite different.

You can get the subtler examples, such as the case often discussed in these circles, of PRCA with erythropoietin. So, Eprex underwent some minor manufacturing changes that increased the incidence of PRCA. That change in incidence is not observable at all in cancer patients--one of the main indications for Eprex. And you could study tens or hundreds of thousands of such patients for years and not detect a difference. But you study--you have to study large numbers, like you

study hundreds of thousands of patients with renal failure, and you do see that difference.

So, one of the issues about biologicals is that they're complex molecules. And part of the impact of that complexity is that they often have--as some of the speakers this morning pointed out--different parts of the molecule--the overall product--that may influence in one area a PK, one binding, one triggering effector mechanisms, another inducing immunogenicity. And I agree in principle that you need to look at differences and determine whether they make a difference, but you do need to be cautious about assuming that because you don't see a difference in one clinical setting, you won't see a difference in a different clinical setting.

DR. SCHWIETERMAN: Next question?

DR. KIM: My name is John Kim for L.G. Life Sciences. I have a comment about some of the comments made by Dr. Fielder from Genentech, that's relating to some transferability of the indications from one to the other, and he has given some

examples about the safety concern in the particular [inaudible] trial?

But the indication you're talking about here is that the one, it has been established already, rather than the new indication. That's why you have given an example is not a [inaudible] example. So we should make a distinction between adding a new indication, whereas another we have established for this new entirely new indications.

DR. HIXON: I just need to make a comment here to get things a little more back on focus. I think we're spending a lot of time talking about the extrapolation of efficacy from one indication to another. And we have several questions in our program that we need to be focusing on a little bit more. And I just wanted to bring us back to those.

The three main questions are actually very broad questions, but they are: what information does a PK study provide? What additional information of value would a PD study provide? And what factors affect study design and establishment of acceptable limits for PK/PD comparison?

Part of my concern is that we're having a discussion that's getting off into what's to be discussed tomorrow in the clinical sessions. And I

think we just need to make sure we're coving PD considerations in this workshop.

[Pause.]

Somebody else was about to make a comment? Was that clinical, or PK/PD?

DR. PARKINSON: Well, speaking as a clinician, it's hard to examine PK/PD in the absence of a clinical setting.

[Laughter.]

PK/PD is in the service of mankind. But, in any case, let's go to that first question.

I think we heard some pretty strong position from Dr. Velagapudi. He's in the back, so he may wish to make additional comments about the feasibility and the needs for PK. And so maybe people could respond to his perspective first.

Please go ahead.

DR. LAWTON: Sorry, it's a slightly different topic.

DR. PARKINSON: Okay.

DR. LAWTON: My name is Alison Lawton. I'm from Genzyme Corporation.

The comment I just wanted to make is with regard to pharmacokinetics we heard earlier in the session this morning, talking about AUC and CMAX.

And I think it's very important for these various types of protein products--different biological products--that plasma levels--it's not the same as doing a comparison for drugs. Often we have to look--many of these proteins act intracellularly, in different organs, and we have to look at the pharmacokinetics and the pharmacodynamics in all of those different sub-components, not just think about the typical pharmacokinetics of plasma AUC and CMAX when we think about this discussion.

DR. PARKINSON: Okay--so an argument for a more detailed PD in the interpretation of the PK/PD comparability.

Additional comments on this topic?

VOICE: [Off mike.] [Inaudible.]

DR. PARKINSON: I'm sorry, I can't--

DR. HIXON: There's not a plenary session, as such, on animal studies. There is a breakout session on pharm-tox issues. However, it is certainly legitimate for us to be discussing the use of animal models for evaluation of PK and PD.

DR. FIELDER: Well, just to keep the discussion going--since that's come up many times--I don't know of any animal model, for PK especially--PK/PD--that's relevant to a human. And

I think especially when you get into a sub-cu formulation, we don't even use--you know, we'll do sub-cu studies in animals to, once again, say "Is there something different we see?" But they're no way predictive of what you'll see in the humans.

And the PD part is very species specific. I mean, growth hormone in humans is radically different from growth hormone in a rat. Pharmodynamics--you know, most of these studies, especially with the antibodies, they don't even cross react in any rodent species, and very few primate species. So it's almost impossible.

So, again, I would say, you know, as good

scientists we should throw that out right away: that animal PK/PD studies are not going to be predictive of humans, and we should just get rid of that. And then the debate can focus more on PK/PD in humans and its utility.

DR. SCHWIETERMAN: But are they useful, again, as comparators? Prediction of clinical effect is one. Detection of differences is another. And the two are integrally related. And, you know, I'm making it very simplistic with these two comments. But, you know, you can use an assay to detect differences even if you're not sure how that outcome measure relates ultimately to the ultimate clinical effect.

Again, I'll say the same way we do it at Genentech: if we see something different in an animal study, we worry. We do not--we don't assume it's okay. We move on to humans for, as far as, you know, major changes. Within-process changes, when we have experience manufacturing for many years, and we know that process very well, it's not such a worry. But something new--especially in

irrelevant species--is not going to predict humans

DR. SCHWIETERMAN: Okay. Thank you.

DR. ROGGE: Paul, I just want to make sure that--I think what I said is consistent with what you just mentioned, when I gave my presentation this morning. I did give some animal examples. Obviously we're not going to get those kind of data from a human trial.

But are you agreeing with me that changes can be occurring in organs in humans? Now they may not go in the same direction that you'd see in an animal species. They might go in similar directions if it's a highly relevant species, but you're not necessarily going to detect it from the PK alone.

DR. FIELDER: [Off mike.] That was very useful.

DR. ROGGE: Okay.

DR. BEN-MAIMON: At the risk of being the sole voice for the generic industry [laughs], I would like to make two comments.

First of all, I think what Bill said is

essential that we keep in mind: we're looking for differences. We're looking for comparability. To say "predict" I think is--you know, for those of us who've worked on new drugs--and I clearly have developed plenty of new drugs in my lifetime, as well--you're looking for things that are going to predict outcome. You're also looking--and probably more importantly--for things that are going to raise a red flag that you may have some reason for concern, and that you may need to either not go ahead, or do something differently.

Here we're talking about products that are already on the market, that are being compared analytically and methodologically to each other. And we're also talking about a continuum. And I think we have to be very careful that we don't get bogged down in the highly complex side, but also remember that there are some simple products like there, like insulin and growth hormone that have been raised earlier today. And there are multiple growth hormones on the market. And the labeling does suggest that they are interchangeable,

although the specimen analogy is not used.

And even if you look back at some of the programs for insulin development, these programs--many of them--have been very limited. And so I think the fact of the matter is that we have to keep in mind two things: we're not developing completely new chemical entities. We are looking for difference. We are proposing doing significant chemical characterization early on to help minimize the concerns about differences.

And, finally, you're looking at PK/PD to reinforce the comfort level you have with the fact that the rate and extent of absorption are the same. That's all this does. It just talks about exposure. That's all PK does. And I think others have brought that up earlier.

The other point I'd like to make is: people keep talking about biologics, and you don't measure them at the site of action, and all these sort of mythical type comments. The fact of the matter is you don't measure drugs at the site of action either. You give them orally, or you give

them subcutaneously, and you measure them in the plasma. You don't go into the knee and look for the NSAID. You don't go to the site of action--into the CNS--and look for the SSRI. You measure them in the plasma because the plasma represents the rate and extent of absorption, and allows to measure--as a surrogate--what's happening at the end organ. And you're comparing two things where you have reasonable characterization.

And there's no reason to expect that biologics should behave any differently.

DR. PARKINSON: Okay. I think we have another opinion.

DR. LAWTON: Yes, I'd like to differ strongly on that point. Specifically, for recombinant proteins, you don't even have to get into biologicals. If you measure plasma level, that doesn't necessarily tell you the level of where you have your protein at the site of action. We have, for example, many enzyme-replacement therapies for lysosomal storage disorders. They are intracellular enzymes. They act intracellularly.

You can measure plasma levels. That does not tell you how much of that protein gets into the cell where it has to act.

And in many cases, the uptake of that protein is dependent, for example, on glycosylation changes. Now you may pick that up on the earlier analytical techniques, but you may not. And you can't assume the plasma levels' being the same will be the same as the site of action for many of these proteins.

DR. FIELDER: I'd like to clarify what's been written down there, and also address the question of predictability.

So--pre-clinical PK/PD, we do use some of those studies to help plan clinical studies? Or some are useful when you do have a relevant model, that we do modeling and scaling and mechanistic modeling to help design clinical trials. We never use that to substitute for a clinical trial. We still do the clinical trial. We just do fewer, we do them smarter.

And then my colleague from the generics

again said that we're not trying to use this data to predict. But isn't that exactly what's being proposed: that we use analytical characterization in vitro, and then a couple simple PK bioequivalence studies, and using that to predict safety and efficacy that's been proven in massive studies.

DR. PARKINSON: Okay. I think that deserves a response. This is good.

DR. BEN-MAIMON: [Off mike.] [Inaudible.]

DR. PARKINSON: Yes. Absolutely. You have the floor--I think is what they say in Washington. [Laughs.]

DR. BEN-MAIMON: I would just respond: we're not using it to predict the clinical outcome of known chemical entities. So if erythropoietin raises hemoglobin, we're not using the PK study to prove that erythropoietin raises hemoglobin. That's already an established fact. It's well in the literature.

What we're using these studies to do is differentiate between different compounds and

determine whether or not there are clinically relevant differences in the exposure for PK. That's all it is.

DR. FIELDER: [Off mike.] You are extrapolating that [inaudible] safety has already been proven--

DR. BEN-MAIMON: Absolutely.

DR. FIELDER: [Off mike.]--and you don't need--

DR. BEN-MAIMON: Absolutely. But you're not using it for a Phase I study, to predict clinical outcome in a Phase III study and establish a clinical endpoint that has not been demonstrated.

DR. FIELDER: [Off mike.] I would say that [inaudible]--

DR. PARKINSON: Could you use the microphone? Just for the record here?

DR. FIELDER: Just to raise some points. Probably we can use Centacor, Remicaid, Genentech's Retuxan--many of these antibodies. In some cases we have infusion reactions that we've never been able to predict preclinically. There's no marker

or PD for that. But others are rare infusion-related reactions, and are--with Receptin, cardiotoxicity--some very rare events. And PK/PD's never going to tell you that. And we don't even know what causes those things--still for Receptin. Unknown--we know it's worse when you combine it with certain chemotherapies. But to actually power a trial to compare these rare events, which we don't understand, would be huge.

So I think, again, we don't know lot about what causes a safety event. I think we know a little about what efficacy is. So to assume, by looking at a molecule we know exactly which attributes cause--are related to safety and efficacy is naive at this time. Because I can't, and I work on these all the time.

DR. STARK: My name is Yatif Stark, from Teva Pharmaceutical in Israel, and I'm having to ask--I'm responsible for innovative drug development, but also I'm here to talk about biologic generic.

And I have several questions to pose.

First of all, if coming from the innovator, innovation and development, sometimes--every batch that we produce is a little bit different from the batch--the previous batch. But still we don't repeat our pharmacokinetic, pharmacodynamic studies. This is one question that I would like to raise.

Additionally, coming from the field of multiple sclerosis, there are three different products on the market; three different interferons. They are different in the dosage form, they are different in the pharmacodynamics. But still, if you look at the overall benefit to the patients, the three of them are very comparable in terms of the clinical benefit to the patient.

So I'm asking the question: what values do we have when it comes to the design of this pharmacokinetic-pharmacodynamic studies, and how much they can contribute to the understanding of the overall clinical benefit to the patient?

DR. SCHWIETERMAN: Thank you very much.

Other questions, responses?

DR. SANDERS: Just to take a little different perspective, and maybe try to answer one of the questions that's in the program--if you are

given the task to say you're going to substitute one product for another, to use them interchangeably, I would certainly want these two products to have identical PK/PD data. That would be very good. That would be a very good thing to look at and be assured that I would be able to substitute product A for product A-prime, or whatever you wanted to call it.

So, in that respect, I think PK/PD studies are very valuable in helping us to establish and provide information that two products are the same. And I would want to have--you know, if I were going to substitute a product, I'd want to see the PK data and say, "Yeah, the PK data is the same." And the criteria to establish that--I think the current bioequivalence are quire acceptable. They're pretty stringent and, in fact, probably as is the case, with some exceptions to that, where you have highly variable drugs, where you have to get into

doing some kind of repeat types of studies in order to understand the physiological variability versus the variability that might be coming from your dosage form, those 80 to 125 parameters are quite good.

And I think it will be very difficult, though, to establish any parameters that are going to be codifiable for pharmacodynamics. They tend to be more variable, and it's going to be difficult to put those--I mean, there was no comment made by Dr. Ahn earlier if, you know, on the PD side, if the insulin parameter that fell outside that boundary, if that, in her mind, meant that those two products were not bioequivalent. But certainly from a PK perspective, I think the current bioequivalence guidelines are quite acceptable, and I would want to see those met for any substitutable type of product.

DR. SIEGEL: Siegel--a couple of points I want to make.

First, the assertion that PK may not matter for some products--I think the example given

was interferon. And I don't know how much data we have comparing various interferons head-to-head, but I can tell you that interferons, over the course of the last decade, have been modified by pegylation, whose sole effect--as far as anyone knows clinically--is to change the PK, not to change the bioactivity. And that has had a profound effect on their dosing on their efficacy in hepatitis.

A classic example from biotechnology occurred in the early days of production of Genentech's TPA, where changes in manufacturing led to changes in PK that had a profound effect. And, in that case, in is clear--and, I think, something we need to look at--that in some products there's going to be a much closer tie-in between PK and efficacy and safety than others. Certainly it's the case in fibrinolytics that modest changes in PK and in levels and in dosing can have profound effects on stroke risk and on survival in heart attach, and in other indications.

So, PK can be quite important.

Another issue that we need to keep in mind that differs here from the small molecule: our speaker from the generics industry noted that the

role of PK is to assure absorption, and that is a critical role, particularly for small molecules which are taken orally, and which when you know if you have the same chemical levels in the blood you know a lot about the likelihood of having the same degree of efficacy.

Of course many of these products are to a large extent given parenterally. There are absorption issues if they're given subcutaneous; less if they're given intravenously. But even when they're given intravenously, there is a lot of value to PK studies, for the reasons that other speakers have mentioned, and that is that there are subtle differences in the molecules, as noted. Sometimes they come up in sensitive analytic testing. Perhaps sometimes they don't. But, even then, one doesn't necessarily know whether they matter or not. And PK testing can reveal differences, and they can reveal differences in

terms of circulatory half-life, but also minor changes in charges, and glycosylation and other--as noted, can cause differences in how they enter tissues.

These sorts of minor changes, if the active ingredient of small molecules also had minor changes would probably be an issue for small molecules as well. But it's just a different issue because they're different here.

Finally, on the issue of animal testing, I would just note one limit of animal testing in certain of these settings is that for some molecules it's quite important not only to know the first dose pharmacokinetic profile, but how the pharmacokinetic profile may change over repeated dosing--which can occur with a lot of molecules, large and small. And animal models are very difficult to use for repeated dosing because almost all biologic products give rise to immunologic responses across species, and after the initial dose or dosing, it's very hard to draw much useful information about PK.

DR. VELAGAPUDI: I hope speakers are allowed to say something, too. [Laughs.]

DR. PARKINSON: Sure. Just give us a

business card. That's all we need. Price of admission.

DR. VELAGAPUDI: Basically I'm hearing the arguments like, you know, in clinical trials we found something. And then the speaker tells: "Well, we found it because the glycosylation is different; glycosylation changes reflected in the candidate, and reflected in toxicology and side effects." But you basically--and I talk about these things philosophically--you already found the difference, and you have a bowl of things in your hand that you know the products are different, and you are trying to eliminate successively how you can eliminate that thing and see the clinical relevance of it.

If the PK doesn't show clinical relevance you go to the next step of showing clinical relevance--okay? So that you go in a stepwise process, but you have the most sensitive tool to

analysis it in your hand first, and you know the answer even before you started that they are different to start with, and then you are trying to figure out what cannot detect that one. That's not the point. What detects that one? Okay? You already have detectible differences to start with. You already know, and then you are going progressively to see: if I change the formulation--the formulation ingredients were different--who in their right mind will think that it's the same?

The formulation is different. You're trying to eliminate whether the formulation difference has any clinical relevance. You're going higher order testing to test that.

Same thing: you are changing product going country to country and setting up different manufacturing plans, and you're coming up with comparability data, and then you already know the minor difference--I'm not saying major differences. You know all the minor differences. In that spectrum of minor differences you're trying to find

out what that relates to. So you're going to the next higher order, PK; next higher order, PD. And if you can't find at that time your likeliness of finding something is getting reduced and reduced and reduced. You're reducing the uncertainty about the comparability.

So that is the pathway we're going at, not the reverse way.

DR. PARKINSON: first of all, any responses to that?

DR. KIM: I'd like to make some comment because what we are talking about, all the biologics in the one kind of breath, whereas we are treating them in a singular manner. But in scientific aspect, as Dr. Ahn mentioned earlier in today's presentation, it depends on the complexity of the protein, we should have some different bar, or that the standard we are going to evaluate. [inaudible] different regulatory aspect, but you can just comment on data. But in scientific terms, that we should have some distinction between some of the simpler to complex, the protein molecules.

DR. SCHWIETERMAN: Questions and comments on that: the notion that, you know, the definitions we use here for comparability ought to be dependent

upon the complexity of the molecule?

Dave.

DR. PARKINSON: Again, I look at everything from a clinical perspective, and it's not the complexity of the molecule as much as it is the clinical complexity; that is, the clinical setting, the therapeutic intent of the use of the molecule, the clinical consequences of a molecule which behaves differently--whatever "differently" means. That's sort of the perspective that I bring to this, which may or may not be related to the actual physical chemical complexity of the molecule. But I think this should be an important topic for discussion.

What do other people think about this? Is it possible to simply put these agents into different categories and have different levels of evidence for the different categories? Is that something one could do?

Go ahead, sir.

DR. KIM: In response to that, let's say there's one innovator is there, and then you're coming out with a new bio-similar or the follow-on biologic. It may be different. But let's say, in the case of several innovators already in the

market, for example in the growth hormone, there is like four or five already in the market, made with a different process, and is a different case for insulin, where there's already several--from several manufacturers already in the market, and they're coming in those cases, your argument about clinical outcome. Because basically they have established a similar clinical outcome from the different formulation, or the different manufacturing processes.

DR. FIELDER: I'd like to just comment on the complexity a bit.

I think as my colleague from ZymoGenetics, lycoproteins are really, in some cases, a family of different proteins. And when you put them together in a simple PK/PD study you tend to get sort of the

average value, which is--you know, the ones that clear fast, the ones that clear slow, the ones that kind of clear in the middle. And so it is sort of a mixture.

So really what we ask the follow-ons to hit: the mid point of that? Or to show that they have the exact same variance, or the exact same extremes of the PK/PD range?

And then again, to get to the simplicity--going to a simple protein again is what growth hormone PK/PD do we have that you would approve a generic on? I mean, if you look on the label of every growth hormone has different pharmacokinetic parameters, especially half-life and absorption. And there's no validated surrogated for growth hormone even. So how would you approve it as a generic?

DR. SCHWIETERMAN: Again, I mean, to take the devil's advocate, if there are differences I think it's very clear that those differences are very difficult to interpret clinically. I guess I would say if there are no differences from

analytical testing, and no differences in PK/PD, what does the audience think about then the utility of predicting comparability and thereby safety and efficacy?

I think many speakers have pointed out very clearly that even the smallest difference, including changes in clinical indication can have profound differences on the product. But what if those differences don't exist? And this is a rhetorical question, I guess, because we don't have the data in front of us. But just theoretically, anyway, could that be used then as a possible path?

DR. FIELDER: Well, I think probably a major issue is we're having a theoretical discussion instead of a scientific one. And, again, can you give one example where that's true--with a protein?

DR. SCHWIETERMAN: Well, I mean, alpha interferon, you take a primary structure that's identical to the innovator, show the identical primary structure and secondary structure, and then show, say, identity between PK/PD. Would you

predict that that could be indicated for the use in hepatitis C?

DR. FIELDER: [Off mike.] [inaudible]

DR. SCHWIETERMAN: Yes, but I'm postulating whether they're the same, actually. Pegylated--the example was pegylation versus non-pegylation.

DR. FIELDER: But most of the pegylated products do go do safety and efficacy studies. So, again--I mean, we made a long-acting growth hormone, and we clearly did Phase III pivotal studies. I mean, the pegylated protein should be doing that.

VOICE: [Off mike.] [Inaudible.]

DR. FIELDER: Correct. But if you could say--what I'm saying is, could you say, "We know enough about growth hormone PK/PD that we could approve on PD. Because I can tell you PD, with growth hormone, if you're going to use IGF-1, you'd never hit a PD bioequivalence.

DR. BEN-MAIMON: first of all, I would never say "never." [Laughs.] Never say "never."

The fact of the matter is, I think with

the growth hormone products is you have products out there that all have been approved by the new drug pathway. They've all been approved through known drug applications. They have not been approved through either 505(b)(2)s or ANDAs--as far as I know. And so I don't think that we've actually challenged the agency with looking at those types of parameters. But I think, after Dr. Ahn's talk this morning, we can see that through PK alone you can actually sequate a nice PK profile for some of these products.

And if you're characterized them--they're not glycosylated, and the amino acid structures are the same, and you've got similar secondary and tertiary structure through all of the various methodologies we have--and you do a PK study, and you meet your 80 to 120 confidence intervals, there's no reason to expect that growth hormone product will perform any differently than the reference.

Now, again, I would say you're going to compare it to one particular growth hormone. It

might not be comparable across all five, because they may not be comparable to each other. But, clearly, to the reference product that you're looking at, they would be comparable, and I think that the agency could approve those products, and I think they have, actually, the regulatory process to be able to do that today.

DR. SCHWIETERMAN: Other comments?

DR. PARKINSON: Do people feel we've adequately answered this third question: the factors affecting study design and establishment of acceptable limits for PK/PD? Particular issues around study design? I've probably heard more argumentation for conduct of PK/PD than not here this afternoon.

So, given that, are there any particular elements with respect to study design that ought to be included? Should not be included?

DR. FIELDER: The only one that I would caution folks against is doing crossover studies. You should do parallel with biologics, especially if they affect the clearance system.

A lot of monoclonal antibodies hit receptors on circulated cells. So if you tried to do a crossover with a Retuxan or something, it

wouldn't be possible--a study design.

So it needs to be case-by-case.

I think growth hormone, insulin, you can do crossovers.

And I think 80-120, that's a pretty high bar already. So it's tough to hit.

But I think--just in closing--I think the problem with these discussions is we have folks at a bit of extreme. A lot of these tools are very valuable in drug development, and we use it a lot to help characterize our drugs within the process of the drug we're making and characterizing and have a history with. And I think where the industry--where we're probably a bit sensitive, is when people then take that and say, "Well, you can apply it to new products that have not gone through the same safety and efficacy."

And, really, the key is: what's right for the patients in being safe? I mean, the

erythropoietin alpha probably had the same PK/PD, but it didn't predict the aplastic anemia of that.

So I think, you know, if we're really concerned about bringing benefit to patients, then we have to put safety at number one. And I don't know how to eliminate the safety concerns without doing safety trials.

DR. ROGGE: Just very quickly--this morning I had mentioned doing repeated measure evaluations rather than necessarily the 80 to 125 approach, but an individual bioequivalence, biocomparability--whatever we want to call it.

Since I've been doing this for 20 years now--when I was in graduate school I was doing bioequivalence studies to support my graduate work--you know this 80 to 125 rule, and what had even preceded that was empirical. Personally, I think there's probably a lot of generic drugs--probably very good generic drugs--that are not on the market now because it was too tight.

And if we consider an individual bioequivalence, where we looked at the reference

product--the innovator product--understood the variability in the PK, and some PD parameter if it was available and well characterized, it would create a much more representative goal-line of sorts for a follow-on product to cross, that would truly be a follow-on, rather than something that may just simply have a similar structure or similar activity.

DR. SCHWIETERMAN: Next question.

DR. XU: My name is Yuan Xu, and I'm Senior Director of Global Regulatory Affairs at Chiron operations.

So after I first say that I'm not a clinician, and also I'm not a PK/PD person, I'm actually an engineer background with CMC.

So the reason I'm interested in coming to give a comment is actually I think there is a fundamental difference between trying to demonstrate comparability of approved product by the originator when they do post-approval changes, and also, you know, trying to compare the product of the originator and the follow-on product. The

reason I say so is when we submit a comparability protocol, not only you do all the characterizations, but another important factor is you compare your manufacturing history. So you're trying to compare your changes with your whole history of your product development.

But when you do a follow-on product, I don't know how and where they're going to get that history background. So one of the things that, from an engineering standard point of view is you do consistency analysis of your whole hundreds of lots of your materials are compared. And also my understanding for when you prepare a BRA for your PK/PD data, all the animal study data, they may come from materials come from different lots.

So here, if you're trying to design a trial to do a comparison of the originator's drug and the follow-on drug, I'm wondering how do you get that variability data to compare? Are you going to design five different trials, compare the data from five different campaigns? Where fro each campaign they have their average product

characterizations. For example, if you--I'm not sure how many of you have actually gone to a lot of CMC type of meetings. In the CMC type of meetings right now, we do a 6-sigma. We do, you know, ongoing product review and re-evaluation, and recalibration or re-tightening of your specs.

So, I'm not sure how you can do PK/PD, or one clinical trial data to compare the whole entire development history of the clinical study.

So, scientifically, I do believe that technology had advanced to the point that you can do follow-on generic drugs, but my point is just: how to hold everybody to the same standard. And if, for the originator's development work, you have to ask them to demonstrate, you know, consistency between Phase I and Phase II, Phase II and Phase III, and Phase III and post-approval. And in general, the post-approval supplement is this big, with plots and plots of every parameter of your manufacturing process to show every critical parameters, they match from campaign to campaign. I just don't quite understand why, for follow-on

protein drugs that you would just need one trial just to demonstrate one plot and that's okay.

So that's my point.

DR. SCHWIETERMAN: Comments on that--on the limits of the single bioequivalence, irrespective of the results, to really capture the totality of the manufacturer's experience? Are those limits such that you can't do that single study and draw the same conclusions that the innovator did? Or are our analytical tools better than that?

Comments?

DR. KIM: My comment is relating to previous the discussion of the 90 percent confidence interval.

I mean, in the case of the PK, probably the 80 to 125 percent seems to be a reasonable one. But when you go to the PD--for example, the IGF-1--probably that criteria, if you do repeat with the innovator's drug, again in the course of a design, many times you may not be able to meet the criteria. And I'm not sure whether it would be reasonable to expect that a follow-on biologic to

fit into that category.

And PK/PD--PK-wise, I think it would be quite reasonable, but in case of PD, meeting that may not be realistic in many cases.

DR. ROGGE: Why is 80 to 125 reasonable?

DR. KIM: The testing used before, so.

DR. ROGGE: Well, why does that make it reasonable?

[Laughter.]

DR. KIM: [inaudible] used before the chemical drug, or the drug approval has been using.

DR. ROGGE: But why does that make it reasonable, though? I mean, in the end we're looking at safety and efficacy and comparability. How do we know that it's, you know--

DR. KIM: [Off mike.] So what is it you're proposing?

DR. ROGGE: Well, I'm not necessarily proposing anything. I'm just saying that 80 to 125 has never been proven to be reasonable. There's a lot of data out there. As I said before, I think, frankly, there's probably a lot of generic drugs

that never made it on the market because it was not reasonable. It was too tight.

I think that, you know, here's our opportunity to stop using technology that's 25 years old, and use some new technology; for example, repeated measures, or individual bioequivalence, or at least something scientifically rational--you know, just as we heard this morning some of the new technology to understand analytically CM and C-wise how we can show comparability.

DR. KIM: In response to that, probably PK-wise, and maybe [inaudible], realistic one. But what I'm trying to say here is that probably we need wide criteria for the PD, compared to the PK, in many cases. That was my argument. And really talking about 80 to 125 percent is one. But that is what is being used.

So under the assumption that PD may need to give more room.

DR. AHN: May I make one comment? You say why 80-125 percent?

When innovator companies make major manufacturing process changes, we use 80-125 percent. So if we use different goal-post of

bioequivalence--what I'm saying is: innovator companies, they use 80-125 percent. That's what agency also use, the 80-125 percent when there is a major manufacturing process change.

DR. SIEGEL: On that question of whether that's the right target, I would just point out that it depends on what you're trying to show with the study.

If the reason you're doing a PK study is the typical small molecule bioavailability-bioequivalence paradigm, then that's probably as tight or even tighter than you need to be. The data would suggest for the large majority--but not all--the large majority of biological products, a 25 percent difference in exposure or dosing does not add up to a clinical difference that is readily measured in clinical trials. So for most of our products, we wouldn't even know if that mattered, but it matters to a

degree that's small enough that it probably doesn't matter for most. There would be some important exceptions.

But that's not the reason--the only reason, at least--that you do those trials. The other reason you do the trials is because there may be differences in the product that are not picked up analytics, or there may be differences in the product that are picked up by analytics but you don't know if they make a difference. But if you see if they make a difference in PK, that could be a clue to other important differences and how they're handled in the body, that are even more important than PK.

In the case of, I think, manufacturing changes, it's largely--by an innovator--it's largely to look for differences that are not being picked up by analytic methods. And I must say I've yet to develop the belief that our analytic methods are sensitive enough that they pick up all of those differences.

So if what you're looking for is, in fact,

a difference--if you're looking for differences in terms of exposure or bioavailability that matter, then you could probably even broaden beyond that. If you're looking for a test to detect differences that might not be picked up other ways, it's somewhat arbitrary where you put the number. But that's a number that's been in use for some period of time, in terms of manufacturing changes, and seems to be one that's reasonably sensitive to differences.

DR. HIXON: Thanks, everybody, for your comments.

It is now three o'clock, and time for our session to be over. I would just like to make a summary statement of what I think I heard, and see if we have some general agreement on a couple of items.

First of all, I think I heard the group agreeing that PK studies are needed; not that PK studies would necessarily be enough. It sounds like the majority of people who have provided a comment have said PK studies are not enough, while

others believe that in some cases they may be enough.

On the issue of the 80 to 125, I think I'm hearing the group as a whole saying: if you make 80 to 125 that is a tight standard, and that should be enough--in terms of the PK studies. Again, no agreement on whether something more than that is needed, but the majority think that PK's not enough, and we need more.

I think I'm also hearing the audience say that PD may be useful in some cases when there is a valid surrogate, but that even PD studies may not be enough to avoid going on to some clinical studies.

Would you all like to add anything more? And does the audience agree that those are the areas where we agree and disagree?

[Pause.]

Thank you very much for your comments and participation.

[Applause.]

[Whereupon, at 3:01 p.m., the breakout

session was concluded.]

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